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Glottic patency during noninvasive ventilation in patients with chronic obstructive pulmonary disease

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ABSTRACT

Background: Non-invasive ventilation (NIV) provides ventilatory support for patients with respiratory failure. However, the glottis can act as a closing valve, limiting effectiveness of NIV. This study investigates the patency of the glottis during NIV in patients with acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD).
Methods: Electrical activity of the diaphragm, flow, pressure and videolaryngoscopy were acquired. NIV was randomly applied in pressure support (PSV) and neurally adjusted ventilatory assist (NAVA) mode with two levels of support. The angle formed by the vocal cords represented glottis patency.
Results: Eight COPD patients with acute exacerbation requiring NIV were included. No differences were found in median glottis angle during inspiration or peak inspiratory effort between PSV and NAVA at low and high support levels.
Conclusions: The present study showed that glottis patency during inspiration in patients with an acute exacerbation of COPD is not affected by mode (PSV or NAVA) or level of assist (5 or 15 cm H_2O) during NIV.

1. Background

Noninvasive ventilation (NIV) can provide inspiratory support for patients with acute respiratory failure. In particular patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD) have been shown to benefit from NIV (Brochard et al., 2002; Chandra et al., 2012; Dickstein et al., 2008). However, in 5–40% of these patients NIV fails (Moretti et al., 2000) and endotracheal intubation is required. Factors for successful NIV include properly timed initiation, a comfortable and well-fitting interface, coaching and encouragement of patients, careful monitoring and a skilled and motivated team (Antonelli et al., 2001). The resulting marker for success is defined as an increasing pH within 1 to 2 h after initiation of NIV (Antonelli et al., 2001; Confalonieri et al., 2005). A major physiological difference between NIV and endotracheal intubation is the involvement of the upper airways. The larynx can act as a closing valve, limiting the effectiveness of delivering inspiratory support under NIV. In normal breathing, the upper airways actively dilate before initiation of inspiratory flow (Ludlow, 2005). This is a highly effective response as narrowing of the upper airways during inspiration would result in elevated inspiratory resistance (Bartlett, 1989). Studies in lambs showed that during NIV with pressure support ventilation (PSV) the activity of the constricting muscle of the glottis (the thyroarytenoid muscle) increases, resulting in decreased upper airway patency (Moreau-Bussiere et al., 2007). In this model, this decreased patency reduces effectiveness of the delivery of tidal volume during NIV. It has been hypothesized that the instantaneous increase in flow in the PSV mode plays an important role in the response of the upper airways during noninvasive ventilation. Neurally adjusted ventilatory assist (NAVA) is a relatively new mode of partially supported ventilation that uses electrical activity of the

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diaphragm (EAdi) to control the ventilator. During NAVA mode, the level of inspiratory support and the cycling of the ventilator is proportional to the electrical activity of the diaphragm (Sinderby et al., 1999). Accordingly, the inspiratory flow pattern follows a more physiological breathing pattern, which may limit upper airway constriction during NIV. Indeed, it was shown in lambs that no glottal constrictor muscle activity is present with NAVA ventilation applied during NIV (Hadj-Ahmed et al., 2012). There are only limited data about the effect of NIV on upper airway patency in humans. In healthy subjects tidal volume is not necessarily increased as a result of increasing noninvasive inspiratory pressure, at least partly due to glottis narrowing (Jounieaux et al., 1995a,b; Parreira et al., 1996b). Today, no studies have been conducted in patients with a clinical indication for NIV. Therefore, it is of interest to compare NAVA mode and PSV mode on upper airway patency in patients with acute exacerbation of COPD. In the current study we aimed to investigate the effects of NIV on upper airway opening in patients with acute exacerbation of COPD, both in PSV and NAVA mode. We hypothesized that patency of the glottis during inspiration decreased with higher inspiratory pressures under PSV. In addition, we hypothesized that NAVA limits the effects of positive pressure on this decreased patency of the glottis.

2. Materials and methods

For this intervention study, we enrolled 8 patients with an acute exacerbation of COPD. Patients were included when meeting the clinical indication for NIV in the Intensive Care Unit (ICU), and having a NAVA catheter in situ (12 French; Maquet Critical Care, Solna, Sweden). This catheter is used to acquire EAdi, measured by nine electrodes placed at the distal end of the catheter (Doorduin et al., 2012; Sinderby et al., 1999). The catheter was positioned at the level of the diaphragm, according to manufacturer's instructions using dedicated software available on the ventilator. This catheter tracks EAdi in all ventilator modes. However, only in the NAVA mode EAdi is used to control the ventilator. Exclusion criteria included upper airway- mouth- or face pathology, recent nasal bleeding (to allow nasal introduction of a video laryngoscope), or pre-existent muscle disease. The protocol was approved by the Ethical Committee of the Radboud University Medical Centre and registered at ClinicalTrials.gov (NCT01791335). All subjects gave their written informed consent.

2.1. Study protocol

The study protocol included four phases: two levels of inspiratory support (5 versus 15 cm H_2O) and two different ventilator modes (PSV versus NAVA) were randomly applied. The gain of NAVA ventilation was set to match peak pressure as delivered in PSV using manufacturer-supplied software.

A flexible video laryngoscope was passed through the facemask and the nostril and positioned ± 2 cm cranial to the vocal cords allowing its continuous visualization. To minimize discomfort during insertion of the video laryngoscope, topical anaesthesia (Xylocaine spray 10%) was applied to the nasal cavity, but care was taken not to apply Xylocaine to the larynx. Each phase started with a run-in period of 30 s in which the subject could familiarize with the ventilator setting followed by at least ten breaths of good quality video recording of the glottis. The rise time in PSV was standardized at 0.05 s. Trigger sensitivity was set at 5% of peak flow (0.5 μV for NAVA) and the inspiratory oxygen fraction was titrated to obtain peripheral oxygen saturation > 95%. Positive end expiratory pressure was kept constant at 5 cm H_2O.

2.2. Data acquisition and analysis

NIV was delivered with a SERVO-i ventilator (Maquet Critical Care, Solna, Sweden). As an interface, a full facemask (Respironics PerforMax, Philips, Best, The Netherlands) was used in all patients.

A unique measurement setup was developed in which parameters from the ventilator and flexible video laryngoscopy were recorded simultaneously, using LabVIEW (version 11.0 National Instruments). Airway flow, airway pressure and EAdi were acquired (f_s = 100 Hz) using Servo Tracker, a software tool for the collection and presentation of performance data from SERVO-i. The data acquired by Servo Tracker was converted with the NI-USB 6229 and NI-USB 6211 modules (National Instruments) to import in LabVIEW.

Real time videos of the glottis (f_s = 25 Hz) were obtained with a fiberoptic flexible bronchoscope (Pentax EB-1170 (11 Fr)). A PCI analog color image acquisition device (NI PCI-1411) acquired the video frames of the bronchoscope in LabVIEW.

Synchronicity of data was ensured in LabVIEW by a phase indicator controlled by the flow of the ventilator. Data were stored and buffered on an external hard disk and analysed offline in Matlab R2017a (The Mathworks, Natick, MA). Of each mode and setting the last 5–10 breaths of good quality of the video were used for analysis. The same time frame for EAdi and flow data was analysed. Good quality was defined as video images allowing the identification of the borders and the anterior commissure of the vocal cords. The aperture of the glottis was assessed for each frame of the video, by measuring the angle formed by the vocal cords at the anterior commissure. A schematic representation of the assessment of the angle is shown in Fig. 1. The contrast between the vocal folds and the rima glottidis was used to detect the edges of the vocal folds, and the angle between two lines fitted through the vocal cords was calculated. The resulting 25 angles per second were averaged over each 3 samples.

2.3. Statistics

Statistical analyses were performed with SPSS 21.0 (SPSS, Chicago, IL). Descriptive statistics were determined for the subject characteristics, given in mean ± Standard Error of the Mean (SEM).

Normality was tested with the Shapiro-Wilk test. Repeated measures

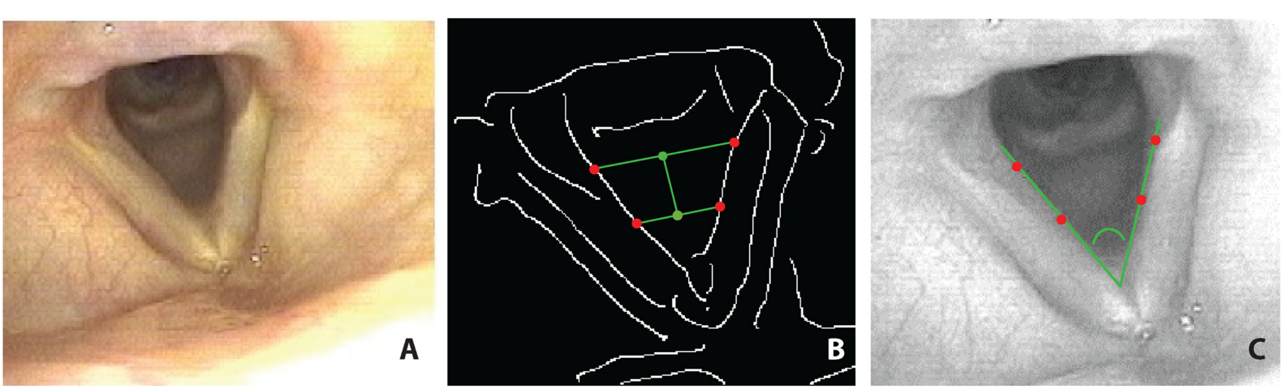

Fig. 1. Schematic representation of angle determination. From video frame (A) to edge detection (B) to determination of glottis angle (C).

Table 1
Patient characteristics, blood values n = 7.

	Mean ± SEM
Age (years)	65.3 ± 3.0
pCO_2 (kPa)	8.4 ± 0.5
pO_2 (kPa)	9.4 ± 1.2
pH	7.34 ± 0.02
Bicarbonate (mmol/L)	33.9 ± 2.5
Base Excess (mmol/L)	6.2 ± 2.4

two-way ANOVA was used to assess the effect of mode (PSV and NAVA) and level (low and high) of ventilation on the mean EAdi of all 8 subjects.

To compare the angle of the glottis during inspiration between the different settings of the ventilator, histograms were made for each setting for each patient, of all the angles during inspiration. Inspiration was defined as EAdi from > 2 μV to 80% of peak EAdi. The median angle was calculated from the histogram, reported for all subjects as mean ± SEM, and the settings were compared with repeated measures two-way ANOVA.

To compare the glottis angle during peak inspiratory effort, as defined by the peak EAdi, the mean angle from −5 to +5 samples of the peak EAdi was calculated for each breath. The angles during peak inspiratory effort were reported as mean ± SEM and compared among the settings with repeated measures two-way ANOVA.

A p value ≤0.05 was considered significant.

3. Results

Eight patients were included in this study (male/female 4/4, patient characteristics in Table 1). Blood gases could not be obtained in 1 patient. Total time for data acquisition for this study was less than 30 min per patient.

Shapiro-Wilk tests showed that mean EAdi, median angle during inspiration and mean angle during peak inspiratory effort were normally distributed. Fig. 2 shows a bar graph of the EAdi of all patients during the 4 phases of the study. As dictated by the protocol, EAdi levels for PSV and NAVA were equal at low ($p = 0.40$) and high ($p = 0.92$) levels of support, showing that the level of inspiratory support was similar for the different modes. As expected, EAdi at PSV low was higher than at PSV high ($p = 0.05$), and EAdi at NAVA low was higher than at NAVA high ($p = 0.01$).

Fig. 3 shows a representative image of the acquired EAdi, flow and angle of the glottis of 1 subject under PSV with a low level of support. The pattern of glottis opening varied within and between subjects; some patients showed cyclic behavior of the glottis as in Fig. 3, related to the breathing cycle, but some showed more chaotic patterns of glottis behavior. The online available additional videos 1 and 2 illustrate this.

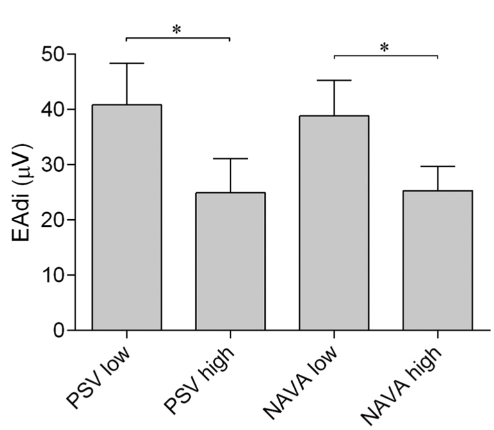

Fig. 2. Bar graph of EAdi of all patients during the 4 phases of the protocol. *significant difference.

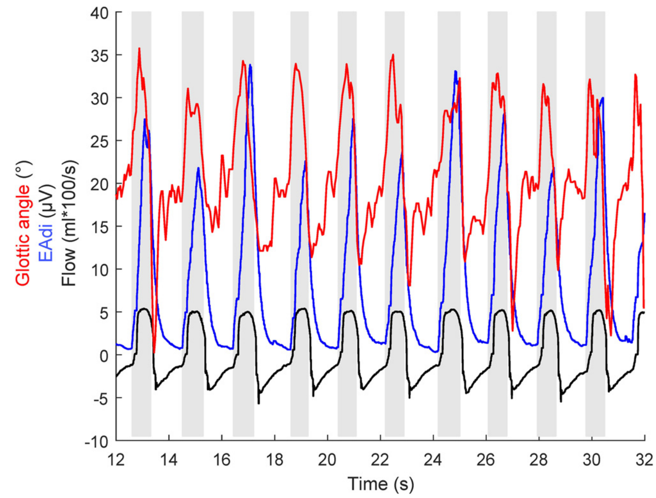

Fig. 3. Example of EAdi, flow and angle of the glottis of 1 subject during 1 setting. Grey areas represent inspiration based on EAdi, from > 2 μV to 80% of peak EAdi.

An example of a histogram with all the angles during inspiration of 1 subject is shown in Fig. 4A. A bar graph of the median angle during inspiration for all patients is shown in Fig. 4B. Mean ± SEM value of the angles during inspiration for all subjects was 43.5° ± 4.1°during PSV low, 43.5° ± 4.5° during PSV high, 43.0° ± 4.8° during NAVA low and 44.3° ± 3.4° during NAVA high. No significant differences were found.

The mean ± SEM value for the glottic angle at peak inspiratory effort for all subjects was 39.1° ± 3.9° during PSV low, 42.8° ± 4.7° during PSV high, 39.6° ± 4.7° during NAVA low and 40.3° ± 3.3° during NAVA high. There was no significant difference between the glottic angle at peak inspiratory effort between the different modes and levels of inspiratory support (Fig. 5).

4. Discussion

This is the first study to evaluate the patency of the glottis during NIV in patients with acute exacerbation of COPD. Specifically, we evaluated the effects of the level of inspiratory support (low and high) and two different ventilator modes (PSV and NAVA) characterized by different flow patterns. We found that neither the level of inspiratory pressure, nor inspiratory flow pattern did affect the patency of the glottis in these patients. These data are in apparent conflict with earlier studies in newborn lambs and healthy subjects (Jounieaux et al., 1995a,b; Moreau-Bussiere et al., 2007; Parreira et al., 1996b).

4.1. Patency of the glottis

The vocal cords largely determine the variations in laryngeal resistance during the normal breathing cycle, and thereby regulate the resistance to airflow of the upper airways (Bartlett, 1989). It is known that in resting or anesthetized animals the vocal cords are abducted during inspiration (Bartlett, 1989). The constricting muscle of the glottis (the thyroarytenoid muscle) is responsible for this contraction in early expiration (Moreau-Bussiere et al., 2007; Roy et al., 2008) and the dilation during inspiration is a result of activity of the dilating muscle (the cricothyroid muscle) (Moreau-Bussiere et al., 2007).

However, studies in newborn lambs showed that the electrical inspiratory activity of the thyroarytenoid muscle increased during NIV. The activity of the cricothyroid muscle on the other hand decreased, while it normally acts as a dilator during inspiration (Moreau-Bussiere et al., 2007). These results suggest that modifications in laryngeal

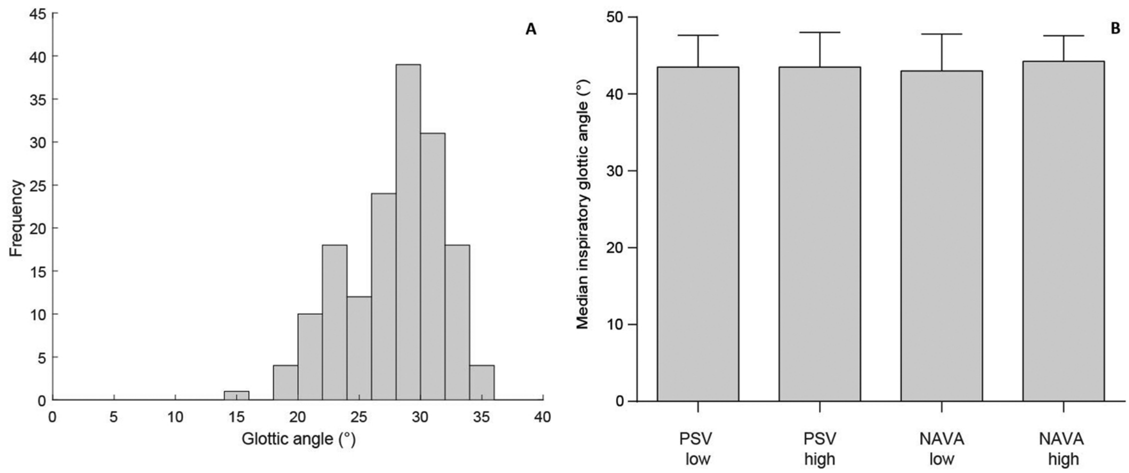

Fig. 4. A Example of a histogram of all angles during inspiration of 1 subject during 1 setting and **B** Bar graph of median angle during inspiration of all patients for the four conditions. No differences between the settings were found.

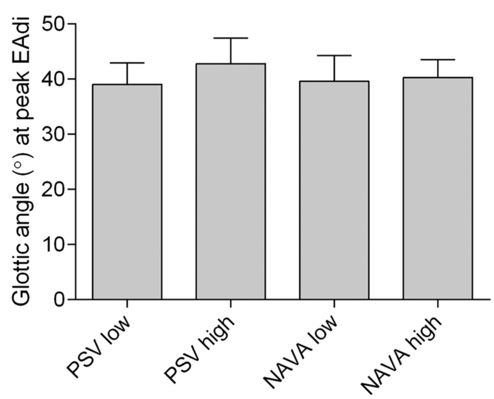

Fig. 5. Bar graph of the glottic angle at peak EAdi for all patients. No differences between the settings were found.

muscle activity regulate active glottal narrowing during noninvasive positive pressure ventilation in lambs (Moreau-Bussiere et al., 2007; Roy et al., 2008). From an evolutionary point of view, closing of the upper airways and the glottis might be an effective protective response, as high pressure delivered to the lungs may induce alveolar overdistension (Roy et al., 2008). However, these glottal responses may negatively affect the efficiency of ventilatory support delivered to the lungs during NIV (Moreau-Bussiere et al., 2007; Roy et al., 2008), result in leaking of the interface of NIV or insufflation of air into the digestive system (Hadj-Ahmed et al., 2012) and thereby potentially influence failure rates.

A better understanding of the behaviour of the glottis of human subjects under different modes and settings of NIV will thus help to obtain better compliance, more effective tidal volumes and thereby higher success rates for NIV.

Several studies analyzed minute ventilation in healthy subjects during nasal two-level positive pressure ventilation in controlled and spontaneous modes (Parreira et al., 1996a,b), and during sleep and wakefulness (Jounieaux et al., 1995a,b). The main findings are more or less consistent with results from lambs. Effective ventilation was not increased or even reduced with increasing levels of inspiratory pressure. Only high inspiratory pressures (20 cm H_2O) in a spontaneous mode resulted in an increased minute ventilation, resulting from an increase of tidal volume (Parreira et al., 1996a). The main factor regulating effective tidal volume during NIV in awake humans appeared to be the additional resistance of the upper airways by closure of the glottis. The glottis narrowed during passive hyperventilation in the absence of respiratory muscle activity, whereas activation of the diaphragm resulted in a significant inspiratory widening of the vocal cords (Jounieaux et al., 1995a). As adding CO_2 to the inspired air could widen the glottis, it was suggested that glottic narrowing could be caused by extreme hypocapnia, to attempt to reverse the hypocapnia induced by NIV (Jounieaux et al., 1995a,b). Glottic narrowing as a result of NIV increased during sleep compared to wakefulness and effective ventilation was also lower during sleep than during wakefulness (Jounieaux et al., 1995b). Besides, a very wide interindividual variability in glottis behavior and effective ventilation is observed, especially during wakefulness (Parreira et al., 1996b). Although in lambs as well as in healthy subjects the glottis narrows with increasing inspiratory pressure during NIV, the results of the current study showed no closure of the glottis during NIV. The current study showed that the glottis of human adults with COPD is not influenced by increasing inspiratory pressure levels during noninvasive pressure support ventilation.

An important explanation for this difference between lambs and humans could be that reflexes alter with maturation and therefore adult population in this study is incomparable by age to the lambs that have been studied earlier (Abu-Shaweesh, 2004; Arsenault et al., 2003; Hadj-Ahmed et al., 2012). Although sheep are, by equality in size and structure of the tissue with human lungs, suitable for various types of research (Meeusen et al., 2009), the human lung still is different in for example anatomy of the lobes. The difference in species could therefore account for differences in behavior of the glottis.

A third important difference is that the reflex pathways in the COPD patients with an acute exacerbation, as in the current study, are probably different from healthy subjects. Mechanical factors such as tidal volume and flow are known to trigger glottis closure, effected by receptors at laryngeal or upper airway level, to avoid hyperventilation in NIV (Jounieaux et al., 1995a). It is probable that the COPD population in the current study has harmed reflex pathways, by their chronic exposure to CO_2 by smoking. The C-fiber receptors, which are excited by chemical stimuli as carbon dioxide and can induce glottis narrowing, are affected in COPD patients by chronic carbon dioxide inhalation (Oppersma et al., 2013), which makes the behavior of the glottis incomparable to healthy subjects.

4.2. NAVA

During PSV the ventilator insufflates air with a constant level of pressure for each breath, with a decelerating flow pattern. The resulting rapid airway pressurization at the onset of inspiration in PSV could be responsible for triggering, in a reflex manner, the inspiratory activity of the glottal constrictor muscles (Hadj-Ahmed et al., 2012). In NAVA ventilation, the pressure rise is thought to mimic the normal progressive recruitment of the diaphragmatic motor units, inducing more synchronous ventilation than NIV with PSV (Sinderby et al., 1999). It is shown that in contrast with nasal PSV, nasal NAVA does not induce inspiratory glottal constrictor muscle activity in nonsedated newborn lambs, even at maximal achievable NAVA levels (Hadj-Ahmed et al., 2012). This absence of inspiratory electrical activity of the thyroarytenoid muscle may partly account for improvement of patient-ventilator interaction and success rates of NIV during NAVA (Hadj-Ahmed et al., 2012; Vignaux et al., 2009). Although NAVA improves glottis patency during inspiration with respect to PSV in newborn lambs, in the current study no difference is found in glottis patency during NAVA. However, as the patency of the glottis is not decreased during PSV, the hypothesized improvement with NAVA is less probable.

4.3. Measurement setup

This study was designed as a proof of concept study, identifying the behavior of the glottis of patients with an acute exacerbation of COPD. A unique measurement setup was created which ensures synchronous data acquisition, in which the level of support and the modus of the ventilator could be analyzed. This is, to our knowledge, the first study in which the behavior of the glottis is synchronously related to the neural drive, represented by the electrical activity of the diaphragm. The studies in healthy subjects discussed above, measured the widest angle of the vocal cords during the inspiratory phase of the mechanical insufflation on a video screen using a flexible protractor (Parreira et al., 1996b). The automated image analysis to calculate the angle of the vocal cords used in the current study, provides a state-of-the-art method for analysis of patency of the glottis. We consider analysis of the angle of the vocal cords considered more reliable than other measures, such as the widest distance between the vocal cords or the surface of the opening. Other measures need the whole glottis without any anatomical structures in view, which appeared practically impossible for more than one breath. However, there were some limitations to this study. The NAVA catheter in situ, which is used for the measurement of EAdi, might influence the behaviour of the glottis. Although the tube does not pass the laryngeal space, it might touch the epiglottis or surrounding tissue and thereby cause reflective non-physiological movement patterns of the glottis. Also the video laryngoscope might influence the physiological behaviour of the vocal cords.

Although the duration of the current study is relatively short, we are confident that if changes would have occurred in glottic patency, these would have been captured within the time frame of the study protocol (maximum 30 min). The change in glottis behaviour is expected to be caused by fast reflexes of the upper airway receptors to changes in the inspiratory flow pattern, which are known to occur in newborn lambs (Hadj-Ahmed et al., 2012; Moreau-Bussiere et al., 2007).

There was no pattern in the behaviour of the glottis, or subgroups to define based on behaviour of the glottis or blood gas characteristics. Although all patients included in this study were in need of noninvasive mechanical ventilation due to COPD, the degree of the illness and probably resulting reflex pathways were different. However, this study is the first to show the high variability in glottis behaviour among patients.

5. Conclusion

In conclusion, in patients with an acute exacerbation of COPD, patency of the glottis during inspiration is not affected by ventilator mode (PSV or NAVA) or the level of inspiratory assist (5 and 15 cm H_2O) during NIV.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resp.2018.07.006.

References

Abu-Shaweesh, J.M., 2004. Maturation of respiratory reflex responses in the fetus and neonate. Semin. Neonatol. 9, 169–180.
Antonelli, M.A., Conti, G.C., Moro, M.M., Esquinas, A.E., Gonzalez-Diaz, G.G.-D., Confalonieri, M.C., Pelaia, P.P., Principi, T.P., Gregoretti, C.G., Beltrame, F.B., Pennisi, M.P., Arcangeli, A.A., Proietti, R.P., Passariello, M.P., Meduri, G.M., 2001. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive Care Med. 27, 1718–1728.
Arsenault, J., Moreau-Bussiere, F., Reix, P., Niyonsenga, T., Praud, J.P., 2003. Postnatal maturation of vagal respiratory reflexes in preterm and full-term lambs. J. Appl. Physiol. 94, 1978–1986.
Bartlett Jr, D., 1989. Respiratory functions of the larynx. Physiol. Rev. 69, 33–57.
Brochard, L., Mancebo, J., Elliott, M.W., 2002. Noninvasive ventilation for acute respiratory failure. Eur. Respir. J. 19, 712–721.
Chandra, D., Stamm, J.A., Taylor, B., Ramos, R.M., Satterwhite, L., Krishnan, J.A., Mannino, D., Sciurba, F.C., Holguin, F., 2012. Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998–2008. Am. J. Respir. Crit. Care Med. 185, 152–159.
Confalonieri, M., Garuti, G., Cattaruzza, M.S., Osborn, J.F., Antonelli, M., Conti, G., Kodric, M., Resta, O., Marchese, S., Gregoretti, C., Rossi, A., Italian noninvasive positive pressure ventilation study, g, 2005. A chart of failure risk for noninvasive ventilation in patients with COPD exacerbation. Eur. Respir. J. 25, 348–355.
Dickstein, K., Cohen-Solal, A., Filippatos, G., McMurray, J.J., Ponikowski, P., Poole-Wilson, P.A., Stromberg, A., van Veldhuisen, D.J., Atar, D., Hoes, A.W., Keren, A., Mebazaa, A., Nieminen, M., Priori, S.G., Swedberg, K., 2008. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur. J. Heart Fail. 10, 933–989.
Doorduin, J., Sinderby, C.A., Beck, J., Stegeman, D.F., van Hees, H.W., van der Hoeven, J.G., Heunks, L.M., 2012. The calcium sensitizer levosimendan improves human diaphragm function. Am. J. Respir. Crit. Care Med. 185, 90–95.
Hadj-Ahmed, M.A., Samson, N., Bussieres, M., Beck, J., Praud, J.P., 2012. Absence of inspiratory laryngeal constrictor muscle activity during nasal neurally adjusted ventilatory assist in newborn lambs. J. Appl. Physiol. 113, 63–70 1985.
Jounieaux, V., Aubert, G., Dury, M., Delguste, P., Rodenstein, D.O., 1995a. Effects of nasal positive-pressure hyperventilation on the glottis in normal awake subjects. J. Appl. Physiol. 79, 176–185.
Jounieaux, V., Aubert, G., Dury, M., Delguste, P., Rodenstein, D.O., 1995b. Effects of nasal positive-pressure hyperventilation on the glottis in normal sleeping subjects. J. Appl. Physiol. 79, 186–193.
Ludlow, C.L., 2005. Central nervous system control of the laryngeal muscles in humans. Respir. Physiol. Neurobiol. 147, 205–222.
Meeusen, E.N., Snibson, K.J., Hirst, S.J., Bischof, R.J., 2009. Sheep as a model species for the study and treatment of human asthma and other respiratory diseases. Drug Discov. Today Dis. Models 6, 101–106.
Moreau-Bussiere, F., Samson, N., St-Hilaire, M., Reix, P., Lafond, J.R., Nsegbe, E., Praud, J.P., 2007. Laryngeal response to nasal ventilation in nonsedated newborn lambs. J. Appl. Physiol. 102, 2149–2157.
Moretti, M., Cilione, C., Tampieri, A., Fracchia, C., Marchioni, A., Nava, S., 2000. Incidence and causes of non-invasive mechanical ventilation failure after initial success. Thorax 55, 819–825.
Oppersma, E., Doorduin, J., van der Heijden, E.H., van der Hoeven, J.G., Heunks, L.M., 2013. Noninvasive ventilation and the upper airway: should we pay more attention? Crit. Care 17, 245.
Parreira, V.F., Delguste, P., Jounieaux, V., Aubert, G., Dury, M., Rodenstein, D.O., 1996a. Glottic aperture and effective minute ventilation during nasal two-level positive pressure ventilation in spontaneous mode. Am. J. Respir. Crit. Care Med. 154, 1857–1863.
Parreira, V.F., Jounieaux, V., Aubert, G., Dury, M., Delguste, P.E., Rodenstein, D.O., 1996b. Nasal two-level positive-pressure ventilation in normal subjects. Effects of the glottis and ventilation. Am. J. Respir. Crit. Care Med. 153, 1616–1623.
Roy, B., Samson, N., Moreau-Bussiere, F., Ouimet, A., Dorion, D., Mayer, S., Praud, J.P., 2008. Mechanisms of active laryngeal closure during noninvasive intermittent positive pressure ventilation in nonsedated lambs. J. Appl. Physiol. 105, 1406–1412.
Sinderby, C., Navalesi, P., Beck, J., Skrobik, Y., Comtois, N., Friberg, S., Gottfried, S.B., Lindstrom, L., 1999. Neural control of mechanical ventilation in respiratory failure. Nat. Med. 5, 1433–1436.
Vignaux, L., Vargas, F., Roeseler, J., Tassaux, D., Thille, A.W., Kossowsky, M.P., Brochard, L., Jolliet, P., 2009. Patient-ventilator asynchrony during non-invasive ventilation for acute respiratory failure: a multicenter study. Intensive Care Med. 35, 840–846.